Add the following claim:

48. The HLA-DR typing process of claim 16, further comprising the step of comparing said hybridization to hybridization between DNA of known HLA-DR type and said DNA sequence.

REMARKS

Applicants have amended the specification to correct various typographical and grammatical errors. In addition, applicants have amended the specification and claims as discussed more fully below in response to the outstanding Office Action. None of these amendments constitutes new matter.

The Amendments to the Specification

Applicants have amended page 1 of the specification to refer to and update the status of parent applications 06/518,393 and 07/902,999, from which the present application claims priority under 35 U.S.C. § 120.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 16-17, 20, 23-24, 26-37 and 40-47 stand rejected under 35 U.S.C. § 112, first paragraph, on the asserted basis that "the specification, while being enabling for DNA sequences of defined sequence composition, does not reasonable provide enablement for sequences defined solely by the property of hybridization, as coding for unspecified portions of proteins, degenerate sequences, or sequences

defined as complementary where no specificity of hybridization is defined." Applicants disagree.

With applicants' disclosure in hand, and in view of knowledge in the art as of the effective filing date of this application, one of skill in the art could readily prepare DNA sequences, other than those of specifically "defined sequence composition", useful for HLA-DR and HLA typing processes and kits. As of applicants' filing date, one of skill in the art would appreciate that, in any specific DNA typing kit or typing process, the useful DNA sequences are those that selectively hybridize to the DNA sequence of interest. Those of skill in the art would also appreciate that a DNA sequence that encodes only a single amino acid, or even two or three amino acids, would not be specific enough to be useful in a DNA typing kit or process. Such a short DNA sequence would hybridize to many DNA sequences that comprise that short sequence. It would also be routine for one of skill in the art to determine the length of a DNA sequence that will specifically hybridize to a particular DNA sequence in the human genome. Thus, once provided with a particular DNA sequence, such as those of "defined sequence composition" recited in the claims, one of skill in the art would readily be able to prepare other DNA sequences or fragments of those DNA sequences that would specifically hybridize to DNA of interest. Neither Wallace et al., Methods in Enzymology, 152, pp. 432-43 (1987) nor

Sambrook et al., in Molecular Cloning, A Laboratory Manual, p. 11.47 (1987), cited by the Examiner, is to the contrary.

By virtue of the specific disclosure of DNA sequences of "defined composition", i.e., the DNA sequences of DR-β-A and DR-β-B, applicants enabled portions of those sequences which hybridize to them, as well as nucleotide sequences which, due to the degeneracy of the genetic code, code for the same polypeptides as those encoded by each specific sequence.

Applicants have also taught that DNA fragments that are identical among the disclosed DNAs, and DNA fragments that comprise regions of mismatch between any two of the disclosed DNAs, will be useful in the typing kits and processes of this invention:

> "In like manner, a collection of 19-mer DNA probes from regions of mismatch and identity among the other HLA-DR-β chain genes may be prepared. Each of the probes will then be specific for a given DR specificity. Hybridization with the collection of probes and controls would, accordingly, allow the rapid and accurate DR typing of large numbers of individuals." (specification, page 32, lines 23-30).

Fragments that are common to the DNA sequences of "defined sequence composition" of this invention will hybridize to the homologous HLA-DR sequences in the genomic DNA of all individuals. Fragments from regions of mismatch will be unique to a particular insert and will only hybridize to the homologous sequences in the genomic HLA-DR

fragment of an individual having a particular HLA-DR type.

As part of their disclosure, applicants determined and compared the nucleotide sequence of DNA sequences DR-ß-A and DR-ß-B (the sequences of which are disclosed in Figures 5A-5D, 7 and 7A) and identified nucleotide sequence differences that, upon expression, code for regions of amino acid mismatch between the polypeptides encoded by those sequences. See, e.g., specification, page 32, lines 1-8 and Figure 9. Specifically, these regions are defined by amino acids 8-15, 26-32 or 72-78, or amino acids 39-45. Applicants further identified the first three regions as polymorphic regions among different HLA-DR-β-chain genes. The fourth region was identified as a conserved region. Once applicants identified such regions, they also made possible portions of the DNA sequences encoding such regions which are capable of specifically hybridizing to said regions, as well as DNA sequences which are complementary or degenerate thereto.

It would be routine for one of ordinary skill in the art to sequence applicants' DR-β-C or DR-β-D DNA inserts and compare their sequence to each other or to the sequence of DR-β-A or DR-β-B. By comparing the sequences, the ordinary skilled person could readily, without undue experimentation, identify specific regions of mismatch that code on expression for one or more amino acid mismatches between the polypeptides coded for by DR-β-A, DR-β-B, DR-β-C

or DR-β-D.

In view of such disclosure, the specification enables those of skill in the art at applicants' filing date to prepare DNA sequences, other than those of specifically "defined sequence composition", useful for HLA-DR and HLA typing processes and kits. As set forth in Sambrook et al.:

> "The hybridization specificity of oligonucleotide probes allows one to use unique sequence probes to screen for genomic clones or cDNAs encoding a specific member of a multigene family, to screen for a new allele when the sequence of one allele is known, to screen for a specific region of a gene, to screen for specific mutants created by site-directed mutagenesis, or to screen libraries with probes whose sequence represents a consensus coding sequence." (p. 433).

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 16-17, 20, 22-24 and 26-47 stand rejected under 35 U.S.C. § 112, second paragraph, on the basis that certain phrases render the claims "vague and indefinite." Applicants have obviated the objection to each phrase by amendment or explanation below.

The Examiner contends that the claim 16 recitation of "areas of hybridization" is indefinite in that the term "areas" lacks proper antecedent basis and is unclear. Applicants have amended claims 16 and 17 to replace the objected-to phrase with the phrase -- detecting hybridization between said DNA and said DNA sequence --.

The Examiner also contends that claim 16 is indefinite in the recitation of "a portion of at least one." Applicants note that the objected-to phrase appears in claim 23, instead of claim 16. As is clear from the portion of the specification relating to DNA fragments that comprise regions of mismatch between the disclosed DNA sequences DR-β-A and DR-β-B, (page 31, line 23 - page 32, line 30), that phrase refers to contiguous sequences of the HLA-DR locus.

The Examiner contends that claim 23 is indefinite in the recitation of "inserts." Applicants have amended claims 23 and 24 to replace that term with the phrase -- sequence --.

The Examiner also contends that claim 23 is indefinite in that "it is not clear what the recitation of 'high criterium' refers to."

The phrase "hybridize under high criterium" is clearly defined in the specification. More particularly, the range of "hybridization criterium" used by applicants to determine the degree of sequence homology between different cDNA clones is defined as "high criterium (5°C below Tm)", "intermediate criterium (24°C below Tm)" and "low criterium (43°C below Tm)" (page 24, line 33 to page 25, line 4). At the time of the present invention, hybridization assays were in general use in molecular biology laboratories. Thus, one of ordinary skill in the art at applicants' filing date would be familiar with the term "Tm", which stands for

temperature of melting and relates to the temperature at which two DNA strands of a hybrid duplex dissociate from one another. See, for example, Molecular Biology, A Laboratory Manual, ed. Maniatis et al., Cold Spring Harbor Laboratory, pp. 387-89 (1982) (copy attached). One of ordinary skill in the art, therefore, would readily understand the phrase "hybridize under high criteria", as used in this application, to mean hybridization at temperatures of about 5°C below the melting temperature of the sample.

The Examiner contends that claim 23 is "indefinite in the recitation of 'comprising a region of mismatch between the polypeptides' in that the term -- mismatch -- is used in the art to refer to nucleic acid sequence differences rather than polypeptide." Applicants have amended claims 23 and 24 to reflect that the region of mismatch is between the recited DNA sequences.

The Examiner contends that claim 23(e) is "indefinite in the recitation of 'coding on expression' as it is unclear how DNA sequences code on expression." Applicants have amended claims 23(e) and 24(c) to replace the objected-to phrase with the phrase -- which, as a result of the genetic code, are degenerate to --. This amendment clarifies that the intended sequences are those which encode portions of the polypeptides encoded by the recited sequences but, due to the degeneracy of the genetic code, differ from those sequences. As of the effective filing

date of this application, the degeneracy of the genetic code (i.e., the fact that most amino acids are encoded by more than one codon) was well known. Applicants have similarly amended claims 31(f), 32(f) and 33(d).

The Examiner contends that claim 30 is "indefinite in the recitation of 'the hybridization control' as the term lacks proper antecedent basis." Applicants have obviated this contention by claim amendment.

The Examiner contends that claim 31 is "indefinite in the recitation of 'specific to' as it is unclear what this term means." Applicants have amended claims 31-33 to replace the objected-to term with the phrase -- specifically hybridizing --.

The Examiner contends that claim 31 is "indefinite in the recitation of 'complementary to' in that it is unclear how complementary is defined." Applicants have amended claims 31-33 to recite that the intended sequences are fully complementary.

The Examiner contends that claim 31 is "indefinite in the recitation of 'DNA sequences which are degenerate to any of the foregoing sequences', in that it is unclear how 'degenerate' is defined." Applicants have amended claims 31-33 to replace the objected-to phrase with the phrase -- which, as a result of the genetic code, are degenerate to --. This amendment clarifies that the intended sequences are those which encode the same regions of the HLA locus as

those which precede them in the claim but, due to the degeneracy of the genetic code, differ from those sequences.

The Examiner contends that claim 38 is "indefinite in the recitation of 'A DNA sequence having the formula' in that it is unclear what is intended by the term 'formula' with regards to a DNA sequence." Applicants have obviated this contention by amending the claims to replace the objected-to phrase with the phrase -- The isolated DNA sequence: --.

Claims 16, 41-42 and 44 stand rejected under 35 U.S.C. § 112, second paragraph, "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps." The Examiner contends that the omitted steps are a step which completes the preamble of the claim, i.e., a comparing step by which the results of the hybridization are actuallly used to determine an HLA-type."

Claims 16 and 41 relate to HLA-DR typing processes including the positive process steps of hybridizing a sample DNA to one of the recited DNA sequences. Claims 42 and 44 add the step of detecting the hybridization. Claims 43, 45 and added claim 48 recite the further step of comparing said hybridization to hybridization between DNA of known HLA-DR type and said DNA sequences. All of these processes are described in the specification at page 31, line 22 to page

32, line 30.

Claims 16, 41-42 and 44 focus on the heart of one facet of applicants' invention -- discovery of the utility of the recited DNA sequences to determine HLA-DR specificity of a given sample at the DNA level, using hybridization techniques. The patentability of applicants' HLA-DR typing processes based on that discovery is independent of steps relating to comparison of areas of hybridization between the sample and the particular DNA sequence to areas of hybridization between DNA of known HLA-DR type and that DNA sequence. Accordingly, applicants are entitled to process claims that do not specify those steps.

The Rejection Under 35 U.S.C. § 101

Claims 23-24, 26 and 31-38 stand rejected under 35 U.S.C. § 101 on the basis that "the claims are directed to DNA sequences without reciting that said sequences are isolated or purified away from their natural source." Applicants have obviated this rejection by amendment, so that the claims incorporate the phrase "essentially free of contaminating HLA-DR factors and other proteins of human origin."

The Double Patenting Rejection

Claims 16, 17, 20, 22 and 22-47 stand rejected under the doctrine of obviousness-type double patenting as

being "unpatentable over" claims 1-22 of United States patent 5,169,941. Applicants stand ready to file a Terminal Disclaimer in this application, if appropriate, upon the Examiner's indication of allowable subject matter.

The Notice of Draftsperson's Patent Drawing Review

Applicants acknowledge the Notice of Draftsperson's Patent Drawing Review, appended to the outstanding Office Action. Applicants stand ready to file Formal Drawings, addressing the informalities cited in the Notice, upon the Examiner's indication of allowable subject matter in this application.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON D.C. 20231, on April 16, 1997

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